

AMENDMENT AND RESPONSE TO OFFICE ACTION

Remarks

Claims 1, 5-19, 23-33 and 44-48 are pending. By this amendment and response, claims 1, 4 and 47 are amended, and claims 2 and 4 are canceled without prejudice or disclaimer. No new matter is added. Applicants note that claim 48 is not included in any of the rejections in the Office Action. Applicants respectfully request clarification on whether claim 48 stands rejected and if so, under which grounds.

Rejection Under 35 U.S.C. § 102

Claims 1, 2, 4-19, 23-33, and 47 were rejected under 35 U.S.C. § 102(a) and 102(e) as anticipated by Oliphant et al. (US 2003/0108900). Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

Legal Standard

To anticipate a claim for a patent, a single prior source must contain all of the claimed elements. Federal Circuit decisions repeatedly emphasize that anticipation is established only if the following three standards are met: (1) all the elements of an invention, as stated in a patent claim, (2) are identically set forth, (3) in a single prior art reference. *See e.g. Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350, 60 U.S.P.Q.2d 1423 (Fed. Cir. 2001).

Analysis

Claim 1 is amended to clarify that the first primer is extended using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce an extended region of the first primer consisting of one to three types of non-termination nucleotides.

As show in sequence below, the primer hybridizes to a special region where the downstream sequence contains only three types of nucleotide. The primer extension is performed in presence of A, T, and C. The G is omitted in the reaction. The primer reaction will stop when the C shows up in the template sequence and the isometric extended product contain only three type nucleotides.

Isometric primer extension of C-Myc gene

```

1081 agceccgagc ccttggtgct ccatgaggag acaccgcca ccaccagcag cgactctgag
1141 gaggaacaag agatgagga agaatcgat gtttttctg tgaaaaagag gcaggtcct
        Isometric Extension product      Primer
    
```

```

1201 ggcaaaaggt cagagtctgg atcaccttct gctggaggcc acagcaaacc tcctcacagc
1261 ccactggtec tcaagagggt ccacgtctcc acacatcagc acaactacgc agegectccc
1321 tcactcgga aggactatcc tctgccaag agggtaagt tggacagtgt cagagtctg
    
```

A second primer hybridizes to the extended region of the first primer. The region of the second primer that hybridizes to the extended region of the first primer also includes one to three types of non-terminator nucleotides.

Claim 47 is similarly amended. Basis for the amendment is found in the specification as originally filed, for example, Figure 3.

AMENDMENT AND RESPONSE TO OFFICE ACTION

The methods of independent claims 1 and 47 require two single primer extension reactions to be performed. The first primer extension reaction requires produces an extended region of the first primer using one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C. Thus, at least one of the four types of nucleotides is absent during the extension reaction. The second primer has a region that hybridizes to the extended portion of the first primer and is also made of one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C. The second primer is then extended to produce extension products, and the extension products are detected.

The Method of Oliphant is Distinguishable from the Claimed Subject Matter

Oliphant Fails to Disclose Formation of Extension Products using One to Three of Four Types of Nucleotides

The Examiner cites to Figure 3 of Oliphant as disclosing the claimed method. Applicants respectfully disagree. Applicants have amended the claims such that the extended region of the first primer consists of one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C. Oliphant fails to disclose at least this element of the claimed subject matter. Therefore, Oliphant cannot anticipate the pending claims.

The Locus Specific Primers of Oliphant Require a Universal PCR Primer Hybridization Site

Figure 3 step 1 and paragraph 352 do not disclose that the extended region of the first primer consists of one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C. The method of Figure 3 is described in ¶¶ 15-17 of Oliphant. Importantly,

¶¶ 16-17 discloses that the method of Figure 3 requires the use of dideoxynucleotides (ddNTPs) and that the primers include universal PCR primer hybridization sites, for example U1, to ultimately PCR amplify an allele of the target nucleic acid. The claimed subject matter does not require the use of ddNTPs in the primer extension reactions or the presence of universal PCR binding sites.

The Method of Oliphant Requires Primers that Are Matched Exactly at the 3' End to Produce Extension Products

Another difference between the method of Oliphant Figure 3 and the claimed subject matter is that Oliphant uses multiple preformed primers having different 3' bases. Only the primers with bases that are exactly matched at the 3' end by the target DNA are extended. ¶ 16. As shown in Figure 3 of Oliphant, preformed primers having different 3' end bases are used to distinguish between alleles. The claimed subject matter does not use multiple primers with different 3' bases to distinguish between alleles. Instead, the claimed subject matter uses one to three of four types of non-terminator nucleotides in primer extension reactions to interrogate a target nucleic acid for the presence of specific allele or nucleotide. For example, one embodiment provides that if the target nucleic includes a "G" at a specific site, the complementary dNTP "C" is omitted from the first primer extension reaction. Thus, the claimed methods change the dNTPs used in the primer extension reactions rather than using multiple preformed primers as disclosed in Oliphant.

The Examiner cited to ¶ 151 as allegedly disclosing that a single non-terminator nucleotide can be added in the primer extension reaction of Figure 3. Applicants respectfully

AMENDMENT AND RESPONSE TO OFFICE ACTION

submit that the Examiner is applying ¶ 151 out of context. ¶ 151 falls under the subheading "Single Base Extension" of ¶ 149. ¶ 150 makes clear that Single Base Extension (SBE) is used to determine the identity of the base at the detection position, and that this technique is referred to as "minisequencing". One of skill in the art would recognize that SBE cannot be used with the method of Figure 3 because a primer extended with only one nucleotide would not serve as a suitable template for a second primer extension reaction. Claim 1 requires that the second primer hybridize to the extended region of the first primer. The second primer cannot hybridize to a single nucleotide extension product.

The Examiner also cites to ¶¶ 352-353. ¶ 352 discloses that the second probe is complementary to the extension product and refers to the method of Figure 2. ¶ 352-353 does not disclose that the second probe or primer consists of one to three of four types of nucleotides. Thus, Oliphant cannot anticipate the pending claims and the rejection should be withdrawn.

Claims 1, 4-19, 23-33, and 47 are not anticipated by Oliphant for at least the reason that Oliphant does not disclose using one to three of four types of non-termination nucleotides to produce a first primer extension product. Oliphant does not disclose using a second primer consisting of one to three of four types of nucleotides to hybridize to the extended region of the first primer extension reaction. Because Oliphant does disclose each element of the claims, Oliphant cannot anticipate the pending claims.

Rejection Under 35 U.S.C. § 103

Claims 44-46 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Oliphant (US 2003/0108900), in view of Wang (EP 1 162 278 A2). Claim 48 is rejected under 35 U.S.C. § 103(a) as obvious over Oliphant et al. in view of Robertson et al. (Trends in Genetics (2000) 16(6):265-271). Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

The Legal Standard for Obviousness

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

- (a) determining the scope and contents of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 US 1, 17-18, 148 USPQ 459,467 (1966). These four factors are traditionally referred to as the Graham factors. The Graham factors were recently affirmed by the U.S. Supreme Court. *KSR Int'l. Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

AMENDMENT AND RESPONSE TO OFFICE ACTION

In response to the KSR decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "Therefore, in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

Additionally, it is well known that references relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., "they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose

AMENDMENT AND RESPONSE TO OFFICE ACTION

among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

Analysis

The combination of Oliphant and Wang does not render claims 44-46 for at least the reason that the combination of references fails to disclose or suggest each element of the claims.

Determination of the Scope of the Prior Art

Oliphant

As noted above, Oliphant does not disclose or suggest a primer extension reaction using one to three of four types of non-termination nucleotides in a first primer extension reaction. Nor does Oliphant disclose or suggest a second primer extension reaction in which a second

AMENDMENT AND RESPONSE TO OFFICE ACTION

primer consisting of one to three of four types of nucleotides hybridizes to the extended region of the first primer extension reaction product.

Oliphant discloses methods for distinguishing between different alleles using primers having different 3' bases. The claimed method modifies the nucleotides used in the extension reaction instead of using multiple preformed primers.

Wang

Wang discloses a method for producing isometric metric primer extension products. Wang does not disclose or suggest a second primer extension reaction in which the second primer consists of one to three of four types of nucleotides and hybridizes to the extended region of the first extension product.

The Combination of Oliphant and Wang Fails to Disclose or Suggest Each Element of the Claims

Wang does not cure the deficiencies of Oliphant. Specifically, Wang fails to disclose or suggest a second primer extension reaction using a second primer having a region complementary to the first primer consisting of one to three types of nucleotides selected from the group consisting of A, T or U, G, and C. Thus, the combination of references fails to disclose or suggest every element of the claims, and the combination cannot render the claims obvious.

Differences Between the Prior Art and Claims 44-46

Oliphant teaches methods of detecting nucleic acids using primers having universal PCR hybridization sites and various 3' bases such that only primers having a base complementary to

the nucleotide of interest are extended. Independent claim 44 uses three of four types of nucleotides to produce first and second extension products, wherein the primer for the second extension reaction consists of the three of four types of nucleotides and hybridizes to the extended region of the first primer extension product. Oliphant uses different primers to distinguish between alleles; whereas the claimed methods use different nucleotide compositions to distinguish between alleles.

Wang discloses methods for producing isometric primer extension products using defined formulations of nucleotides. Wang fails to disclose or suggest a method for detecting nucleic acids by performing a first primer extension reaction using three of four types of nucleotides and then performing a second primer extension product reaction using a second primer that has region consisting of three of four nucleotides and hybridizes to the extended portion of the first extension product.

Resolving The Level Of Ordinary Skill In The Pertinent Art

The level of ordinary skill in the art would be molecular biologist having at least an undergraduate degree in molecular biology or equivalent science and at least one year of laboratory experience performing primer extension reactions.

Modifying Oliphant with Wang Changes Renders the Method of Oliphant Inoperable

One of ordinary skill in the art would not be motivated to combine the teachings of Oliphant and Wang because omitting one type of nucleotide as taught by Wang would not enable the extension products of Oliphant to be PCR amplified. It is well known in the art that PCR

AMENDMENT AND RESPONSE TO OFFICE ACTION

amplification requires all four types of nucleotides to amplify a target nucleic acid. Thus, the combination of Oliphant with Wang cannot render the claims obvious.

With regard to claim 48, as discussed above, claim 47 is not disclosed or suggested by Oliphant. Robertson et al. fail to cure the deficiencies of Oliphant. Accordingly, the combination of Oliphant with Robertson et al. fails to render claim 48 obvious.

Double Patenting Rejection

Claims 1, 2, 4, 5, 7-19, 23-33, and 44-46 are rejected under the judicially created doctrine of obviousness type double patenting over U.S. Patent No. 6,824,980 in view of Oliphant et al. Although Applicants disagree, Applicants enclose a Terminal Disclaimer disclaiming any term extending beyond that of the '980 patent. Therefore, the rejection is overcome.

U.S.S.N. 10/757,263
Filed: January 14, 2004
AMENDMENT AND RESPONSE TO OFFICE ACTION

Conclusion

Allowance of claims 1, 5-19, 23-33 and 44-48 is respectfully solicited. However, in the event that the Examiner is inclined to reject any of the claims in this application, Applicants respectfully request an interview with the Examiner prior to the issuance of a further Office Action.

Respectfully submitted,

/Charles Vorndran/
Charles Vorndran
Reg. No. 45,315

Date: May 29, 2007

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)